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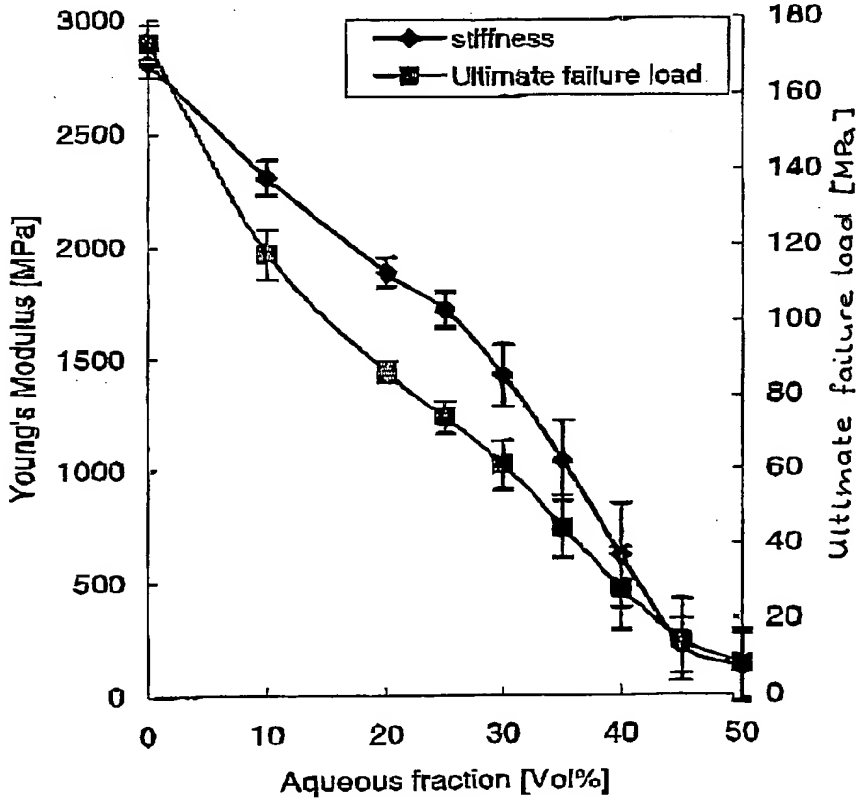
(54) Title: INJECTABLE BONE-REPLACEMENT MIXTURE



(57) Abstract: An injectable mixture for substituting bone tissue in situ comprises: A) a two-component powder/liquid bone cement which upon mixing forms a selfhardening cement paste; and B) a third component consisting of a liquid which essentially is non-miscible with the cement paste and which is suitable to be washed out after hardening of said mixture in situ, resulting in a porous bone substituting material, whereby C) said injectable mixture comprises an X-ray contrast agent which is an organic substance.The injectable bone substitute material for bone augmentation has adaptable mechanical properties, an optimal radio-opacity without any inorganic X-ray contrast agent and therefore good biocompatibility.

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INJECTABLE BONE-REPLACEMENT MIXTURE

The invention relates to an injectable mixture for substituting bone tissue in situ, in particular for bone augmentation, such as vertebroplasty, femoroplasty (femoral neck augmentation), humeroplasty (humerus head augmentation) according to the preamble of claim 1.

Polymethylmethacrylate (PMMA) bone cement is by far the most frequently used material known in the art of bone augmentation (e.g. percutaneous vertebroplasty). However, there are serious complications in the use of this material such as cement leakage, monomer toxicity, necrosis, and increased fracture rate of the adjacent vertebrae.

By "cement leakage" is meant the leakage of the injected cement paste out of the bone, in particular into the spinal canal, which can provoke neurological damages such as paralysis. The injected cement can also go into blood vessels and provoke an embolism.

As is well known PMMA cement hardens according to a very exothermic reaction. Therefore, the tissues surrounding the injected cement might become heated up at temperatures high enough to provoke tissue necrosis.

The increased fracture rate mentioned above is caused by an inadequate stiffness of the augmented segment within an osteoporotic spine and results from the fact that PMMA cement is much stiffer than cancellous bone. Therefore, the whole biomechanical stability of the vertebrae is modified by the presence of the PMMA cement. These biomechanical changes lead to an increased incidence of fractures of the vertebrae adjacent to the augmented vertebrae. The possible countermeasure of prophylactic augmentation of the adjacent levels has the drawback that it enlarges the intervention and enhances the risk for additional cement leakage.

From US-A-4 093 576 deWijn it is known to mix a doughy bone cement mixture with a highly viscous aqueous gel to form a dispersion of the bone cement with the gel. This mixture is used for anchoring prosthetic joints into bone, namely to increase the bone-cement interface for an increased anchorage of the prosthesis. Since the gel is water

soluble, it will be washed out after implantation in the body leaving back a porous bone cement. One of the major drawbacks of the material according to US-A-4 093 576 deWijn is the use of metallic ions as X-ray contrasting agent. Such particles are incorporated into the gel and therefore, these particles are washed away and can provoke compatibility problems.

In the materials according to the state of the art which use inorganic X-ray contrast agent, like zirconium dioxide and barium sulfate in solid particle form there is a phase separation between the MMA and the inorganic, solid X-ray contrast agent. This is probably caused because of the hydrophilic properties of the heavy metal ions in combination with the hydrophobic properties of the PMMA. If water is used as third component in the mixture the inorganic X-ray contrast agent selectively accumulate into the aqueous phase. Therefore, complications may occur for clinical applications because of the washing-out of the aqueous phase. Clinical follow-up is not possible because of the lacking radio-opacity after a certain time of washing-out.

Inorganic X-ray contrast agents ($BaSO_4$, ZrO_2) selectively accumulate into the aqueous phase and thus are washed-out into the blood circulation within a few days with the risk of embolism and toxic reactions. In this context it has to be observed that he amount of X-ray contrast agent necessary for the injection control in bone augmentation is very large, i.e. much larger than for other applications such as the fixation of hip prosthesis for example according to US-A-4 093 576 deWijn. Washing out of such a large portion of inorganic heavy metal ions in the patient may be very dangerous or even perilous.

On this point, the invention intends to provide remedial measures. The invention is based on the objective of providing an injectable self-hardening mixture which upon hardening a subsequent washing out of material in situ results in a porous bone substitute material having a reduced stiffness compared to a conventional hardened PMMA bone cement and which has an optimal radio-opacity.

The invention solves the posed problem with a mixture that displays the features of claim 1 as well as with the use of such as mixture that displays the features of claims 33 and a method for preparing such an injectable mixture that displays the features of claim 38.

The injectable bone substitute material for bone augmentation has adaptable mechanical properties, an optimal radio-opacity without any inorganic X-ray contrast agent and therefore good biocompatibility.

The advantages achieved by the invention are essentially to be seen in the fact that, thanks to the mixture according to the invention:

a) An optimal biocompatibility is achieved by using an organic X-ray contrast agent, preferably one certified for parenteral application. Organic X-ray contrast agents (preferably iodine-containing) can be prepared as an aqueous solution and therefore can directly replace the entire aqueous phase. To allow a follow-up control after washing-out of the aqueous phase preferably a lipophilic X-ray contrast agent can be used additionally with selective accumulation into the PMMA phase;
b) The high radiopacity of the injectable mixture makes it clearly radiologically visible so that cement extravasation during injection can be prevented;
c) The stiffness of the bone substitute material obtained in situ is reduced and adaptable to the properties of osteoporotic bone, hence the risk of fractures of the vertebrae adjacent to the augmented vertebra is lower;
d) A lower amount of polymerization heat is released during polymerization; hence the risk of bone necrosis is lower;
e) The optimal handling and extensive experiences in the application of PMMA based powder/liquid bone cements for vertebroplasty can be utilized.

In a preferred embodiment the X-ray contrast agent is a liquid substance or a solid substance dissolved in a liquid solvent, preferably in water. The X-ray contrast agent may be based on iodine and preferably is chosen from the following group of substances: iopromidum, iopamidol, aminotrizoate acid, iotroxin acid, iopodin acid, iomeprol, iodamid, ioxithalamate, iothalamate, ioxaglin acid and lipiodol (iodised ethyl ester of the fatty acids of poppy-seed oil).
The iodine-based X-ray contrast agent may be used in an aqueous solution, preferably in a concentration of 30 to 80 weight % . The injectable mixture may comprises at least 5 weight %, preferably at least 20 weight % of said X-ray contrast agent.

In a further embodiment the viscosity of said third component is lower than 200,000 centipoise. The viscosity of said third component may be lower than 100,000 centipoise,

preferably lower than 20,000 centipoise. Typically the viscosity of said third component is 300 centipoise.

In a further embodiment the viscosity of said third component purposefully is comprised between 1,000 and 100,000 centipoise, preferably between 2,000 and 50,000 centipoise.

In a further embodiment the viscosity of the injectable mixture measured 4 minutes after mixing of all components is in the range of 200,000 to 300,000 centipoise. Below 200,000 centipoise the injected mixture tends to leak from the treated bone; above 300,000 centipoise the force required to inject the mixture becomes rapidly too large to enable manual injection.

In a preferred embodiment said two-component bone cement is based on a polyacrylic cement (in particular a polymethacrylic cement) or a calcium phosphate cement. Said two-component bone cement is preferably a powder/liquid system base on polymethylmethacrylate (PMMA) powder and monomethylmethacrylate (MMA) liquid with a polymerization catalyst and a polymerization accelerator.

The third component may comprise water and discrete particles of a water-soluble solid substances. Said water-soluble solid substance may be taken from the group of polysaccharides, in particular: chondroitin sulfate, carboxymethyl cellulose, hydroxyethylmethylcellulose, fucan, carregeenan, dextran, heparin, heparan sulfate, hydroxyethlycellulose (HEC), hydroxypropylmethyl cellulose, sodium alginate, chitosan or a hyaluronate.

In a further embodiment said third component is an aqueous hyaluronate solution with a concentration of 0.1% to 5.0%, preferably of 1.0 % to 2.0 %. Typically the concentration may by 0.5 %.
The molecular weight of said hyaluronate should be at least 500,000 Daltons, preferably at least 800,000 Daltons. The molecular weight of said hyaluronate should be below 5,000,000 Daltons, preferably below 2,000,000 Daltons. Typically the molecular weight of the hyaluronate used is 1,100,000 Daltons.
Said water-soluble solid substance may be taken from the group of gelatin or collagen.

In a further embodiment said third component is a hydrophobic liquid which preferably is selected from the group of:
ricinoleic acid ($C_{17}H_{33}OCOOH$), linoleic acid ($C_{17}H_{31}COOH$), palmitic acid ($C_{15}H_{31}COOH$), palmitoleic acid ($C_{15}H_{29}COOH$), stearic acid ($C_{17}H_{35}COOH$), linolenic acid ($C_{17}H_{29}COOH$), arachidic acid ($C_{19}H_{39}COOH$), myristic acid ($C_{13}H_{27}COOH$), lauric acid ($C_{11}H_{23}COOH$), capric acid ($C_9H_{19}COOH$), caproic acid ($C_5H_{11}COOH$), oleic acid ($C_{17}H_{33}COOH$), caprylic acid ($C_7H_{15}COOH$), erucic acid ($C_{21}H_{41}COOH$), butyric acid (C_3H_7COOH), ethyl myristate ($C_{13}H_{27}COOC_2H_5$), ethyl oleate ($C_{17}H_{33}COOC_2H_5$), ethyl palmitate ($C_{15}H_{31}COOC_2H_5$), ethyl linoleate ($C_{17}H_{31}COOC_2H_5$), ethyl laurate ($C_{11}H_{23}COOC_2H_5$), ethyl linolenate, ($C_{17}H_{29}COOC_2H_5$), ethyl stearate ($C_{17}H_{35}COOC_2H_5$), ethyl arachidate ($C_{19}H_{39}COOC_2H_5$), ethyl caprilate ($C_7H_{15}COOC_2H_5$), ethyl caprate ($C_9H_{19}COOC_2H_5$), ethyl caproate ($C_5H_{11}COOC_2H_5$), ethyl butyrate ($C_3H_7COOC_2H_5$), triacetin ($C_9H_{14}O_6$), alpha tocopherol ($C_{29}H_{50}O_2$), beta tocopherol ($C_{28}H_{48}O_2$), delta tocopherol ($C_{27}H_{46}O_2$), gamma tocopherol ($C_{28}H_{48}O_2$), benzyl alcohol (C_7H_8O), benzyl benzoate ($C_{14}H_{12}O_2$), methylphenol (C_7H_8O), di-n-butyl sebacate ($C_{18}H_{34}O_4$), diethylphthalate ($C_{12}H_{14}O_4$), glyceryl monooleate ($C_{21}H_{40}O_4$), lecithin, medium chain triglycerides, mineral oil, petrolatum, and liquid paraffines.

In a further embodiment said mixture is divided into a powder component and a liquid component, whereby

A) said powder component comprises the powder component of said two-component bone cement and a polysaccharide in powder form; and
B) said liquid component comprises the liquid component of said two-component bone cement and an aqueous solution of said X-ray contrast agent.

In a further embodiment said third component is a freshly mixed calcium phosphate cement paste.
In a further embodiment the size of all powder particles of said mixture are smaller than 300 micrometers, preferably smaller than 250 micrometers Purposefully the size of at least 80 % of all powder particles is in the range of 50 to 300 micrometers, preferably in the range of 80 to 250 micrometers. This makes the mixture specially suitable for injection into porous bone structures.

The injectable mixture should harden within 7 to 10 minutes, preferably within 8 to 9 minutes after mixing of its components. This keeps time of anesthesia at a minimum and allows immediate patient weight bearing.
Purposefully the hardened mixture has a Young's modulus of elasticity in the range of 10 to 2800 MPa, preferably in the range of 100 to 700 MPa.

The injectable mixture may further comprise an osteoinductive substance, preferably in its third component. Said osteoinductive substance may be chosen from the following group of substances:

a) bone morphogenetic proteins, preferably BMP2, BMP4 or BMP7;
b) growth factors, preferably TGFb-3 (transforming growth factor) or IGF-1 (insulin-like growth factor);
c) plateled-derived growth factor (PDGF);
d) parathyroid hormone (PHT) and parathyroid hormone-related protein (PTHrP);
e) sexual hormones, in particular estrogen; and
prostaglandin.

The injectable mixture may further comprise an antiresorptive substance, preferably in its third component. An antiresorptive substance means a drug, which inhibits resorbtion, i.e. the bone is inhibited to resorb cells. The advantages obtained by the inclusion of such a drug is the possibility of local treatment of osteoporosis which prevents further resorption of the vertebra. Said antiresorptive substance can be a bisphosphonate.
The injectable mixture may further comprise an anabolic substance, a parathyroid hormone (PTH) or an estrogen. An anabolic substance means a drug which generates more bone production, i.e. the bone producing cells are activated.
The injectable mixture may further comprise a hydrogen pump inhibitor, preferably basilomycin A1. The advantage obtained by the inclusion of such a hydrogen pump inhibitor lies in the fact said these drugs are not well applicable systemically and therefore an advantage is obtained by applying them locally.

The injectable bone cement mixture which becomes porous after hardening in situ due to the washing out of its third component is especially useful for treating osteoporosis,

for filling bone defects but also as a carrier for an agent for the treatment of osteoporosis.

A possible method for preparing such injectable mixtures for substituting bone tissue in situ may comprise the following steps:

A) the two components of the bone cement are mixed first; and subsequently
B) the obtained mixture is dispersed in the third component.

Another method would comprise the following steps:

A) the two components of the bone cement are mixed first; and subsequently
B) the third component is dispersed in the mixed two-component bone cement.

Still another method would comprise the following steps:

A) Mixing separately a two-component powder/liquid bone cement;
B) Mixing separately a two-component calcium phosphate cement;
C) Adding the separately mixed and still pasty two-component calcium phosphate cement to said separately mixed and still pasty two-component bone cement.

According to a particular embodiment of such methods said third component can be dispersed into the two-component bone cement in such a way that the mean diameter of droplets of the third component dispersed in the two-component bone cement is less than 1 mm, preferably less than 0.5 mm.

The quantity of the injectable mixture to be used for substituting bone tissue in situ depends on the application. In the case of vertebroplasty the quantity is in the range of 2 – 10 ml. In the case of femoroplasty, the injected volumes are very large, namely up to 40 ml. Especially in this latter application the mixture according to invention has the advantage over conventional materials to exhibit a relatively low temperature rise due to the setting reaction.

The invention and additional configurations of the invention are explained in even more detail with reference to the following examples and having reference to the accompanying figures in which:

Fig. 1 shows the mechanical properties of open-porous cylindrical samples of the hardened mixture according to the invention with different amount of aqueous fraction;

Fig. 2 shows the pore size dependence of the open-porous cylindrical samples of the hardened mixture according to the invention on mixing time of the mixture (top left to bottom right: 30s, 60s, 90s, 120s); and

Fig. 3 shows the mixing time dependency of the mechanical properties of the biphasic cylindrical samples and distilled water with 10 weight % hydroxypropylmethylcellulose with different amounts of the aqueous fraction, i.e. porosity (P indication the porosity = aqueous fraction) and with different mixing times

Example 1 (laboratory)

a) Composition of the first component
(powder component of the two-component bone cement):
98.2 weight-% of polymethylmethacrylate (PMMA) as filler
1.8 weight-% of benzoyl peroxide as polymerization catalyst
b) Composition of second component
(liquid component of the two-component bone cement):
98.0 weight-% of methylmethacrylate (MMA) as curing monomer
2.0 weight-% of N,N-dimetyl-p-toluidine as polymerization accelerator
c) Composition of third component
2 weight-% of hyaluronic acid
98 weight-% of iopromidium as X-ray contrast agent

The porosity of the mixture to be injected is achieved by manual mixing of the highly viscous aqueous fraction represented be the third component to the liquid component (PMMA) of the two-component bone cement. The increased water viscosity is obtained by producing a 2% aqueous solution of hyaluronic acid. The mixing procedure ran in the following manner. Firstly the PMMA powder (powder component of two-component bone cement) and the specific amount of hyaluronic acid (to get a 2% solution) were homogeneously mixed. Than the specific amount of water and - before further mixing -

the MMA monomer liquid was added. Manual mixing was done for different durations between 60s and 150s to allow more or less spontaneous phase separation between the acrylic and the aqueous phase during the polymerization process. The porosity was assumed to comply with the aqueous fraction.

Cylindrical samples were produced for the mechanical testing of the modified cement. Commercial 2cc syringes were prepared to serve as cast by cutting off the outflow end. The cement was filled into the syringes by cement injection through a 10cc syringe. The 'casting' syringes were stored vertically during the polymerization for at least 120 min. before pressing out the samples. The environment temperature was 21.5 to 22.0°C. The resulting cylindrical samples had a diameter of 9.54 ± 0.08 mm. The samples were ground within a special adapted steel cast to the length of 16.10 ± 0.09 mm with exactly horizontal tops. The aqueous phase including the whole fraction of the X-ray contrast agent was washed out with water for 60-72h to achieve an open-porous structure of the hardened cement. The samples were stored into water (22.0°C) just until the mechanical testing but not longer than one week.

As represented in Fig. 1 the mechanical properties (stiffness measured as Young's Modulus in MPa) and ultimate failure load (measured in MPa) of these samples depend on the amount of the aqueous fraction (in Vol. %).

As shown in Fig. 2 the mixing time importantly influences the pore size. The mixing time influences further the mechanical properties (measured as Young's modulus in MPa) of the hardened material. Several graphs for different degrees of porosity (P in %) are represented.

Example 2 (Clinical application)

The identical material of example 1 was mixed and 10 – 15 ml were injected into the lower thoracic spine of a female cadaver. Injectability, radio-opacity and distribution of the biphasic PMMA-water-compound material were comparable to the commonly used PMMA cements (here Vertebroplastic®, DePuy). A homogenous distribution of the whole compound without any phase-separation was seen microscopically. Mechanical

compression testing of the intact (and cement filled) vertebral bodies showed an increased failure load compared to the non-treated vertebrae. However, the stiffness did not increase in the same amount as for unmodified PMMA cements.

Example 3 (laboratory)

a) Composition of the first component
(first component of the two-component calcium phosphate cement):
10 g if alpha tricalcium phosphate ($Ca_3(PO_4)_2$),
0.5 g of Na_2HPO_4
4 ml of water

b) Composition of second component
(second component of the two-component calcium phosphate cement):
6.5g beta tricalcium phosphate ($Ca_3(PO_4)_2$),
3.5 g monocalcium phosphatemonohydrate ($Ca(H_2PO_4)_2 . H_2O$)
0.125 g $Na_2H_2P_2O_7$, and
4 ml of a 0.1M magnesium sulfate solution.

c) Composition of third component
97 weight-% of Lipiodol® (iodised ethyl ester of the fatty acids of poppy-seed oil).
3 weight-% of hyaluronic acid

Claims

1. Injectable mixture for substituting bone tissue in situ, said mixture comprising:

A) a two-component powder/liquid bone cement which upon mixing forms a self-hardening cement paste; and

B) a third component consisting of a liquid which essentially is non-miscible with the cement paste and which is suitable to be washed out after hardening of said mixture in situ, resulting in a porous bone substituting material,

characterized in that

C) said injectable mixture comprises an X-ray contrast agent which is an organic substance.

2. Mixture according to claim 1, characterized in that the X-ray contrast agent is a liquid substance or a solid substance dissolved in a liquid solvent, preferably in water.

3. Mixture according to claim 1 or 2, characterized in that the X-ray contrast agent is based on iodine and preferably is chosen from the following group of substances: iopromidum, iopamidol, aminotrizoate acid, iotroxin acid, iopodin acid, iomeprol, iodamid, ioxithalamate, iothalamate, ioxaglin acid and Lipiodol® (iodised ethyl ester of the fatty acids of poppy-seed oil).

4. Mixture according to claim 3, characterized in that the iodine-based X-ray contrast agent is used in an aqueous solution, preferably in a concentration of 30 to 80 weight %.

5. Mixture according to one of the claims 1 to 4, characterized in that the injectable mixture comprises at least 5 weight %, preferably at least 20 weight % of said X-ray contrast agent.

6. Mixture according to one of the claims 1 to 5, characterized in that the viscosity of said third component is lower than 200,000 centipoise.

7. Mixture according to claim 6, characterized in that said viscosity of said third component is lower than 100,000 centipoise, preferably lower than 20,000 centipoise.

8. Mixture according to claim 6 or 7, characterized in that said viscosity of said third component is between 1,000 and 100,000 centipoise, preferably 2,000 and 50,000 centipoise.

9. Mixture according to one of the claims 1 to 8, characterized in that the viscosity of the injectable mixture measured 4 minutes after mixing of all components is in the range of 200,000 to 300,000 centipoise.

10. Mixture according to one of the claims 1 to 9, characterized in that said two-component bone cement is based on a polyacrylic cement, preferably polymethacrylate cement or a calcium phosphate cement.

11. Mixture according to claim 10, characterized in that said two-component bone cement is a powder/liquid system base on polymethylmethacrylate (PMMA) powder and monomethylmethacrylate (MMA) liquid with a polymerization catalyst and a polymerization accelerator.

12. Mixture according to one of the claims 1 – 11, characterized in that said third component comprises water.

13. Mixture according to one of the claims 1 to 12, characterized in that said third component comprises discrete particles of a water-soluble solid substance.

14. Mixture according to claim 13, characterized in said water-soluble solid substance is taken from the group of polysaccharides.

15. Mixture according to claim 14, characterized in said that polysaccharide is chondroitin sulfate, carboxymethyl cellulose, hydroxyethylmethylcellulose, fucan, carregeenan, dextran, heparin, heparan sulfate, hydroxyethlycellulose (HEC), hydroxypropylmethyl cellulose, sodium alginate, chitosan or a hyaluronate.

16. Mixture according to claim 15, characterized in said third component is an aqueous hyaluronate solution.

17. Mixture according to claim 16, characterized in said the concentration of said aqueous hyaluronate solution is in the range of 0.1% to 5.0%, preferably of 1.0 % to 2.0 %.

18. Mixture according to claim 17, characterized in said the molecular weight of said hyaluronate is at least 500,000 Daltons, preferably at least 800,000 Daltons.

19. Mixture according to claim 17 or 18, characterized in said the molecular weight of said hyaluronate is below 5,000,000 Daltons, preferably below 2,000,000 Daltons.

20. Mixture according to claim 13, characterized in said water-soluble solid substance is taken from the group of gelatin or collagen.

21. Mixture according to one of the claims 1 to 20, characterized in said third component is a hydrophobic liquid.

22. Mixture according to claim 21, characterized in said hydrophobic liquid is selected from the group of : ricinoleic acid ($C_{17}H_{33}OCOOH$), linoleic acid ($C_{17}H_{31}COOH$), palmitic acid ($C_{15}H_{31}COOH$), palmitoleic acid ($C_{15}H_{29}COOH$), stearic acid ($C_{17}H_{35}COOH$), linolenic acid ($C_{17}H_{29}COOH$), arachidic acid ($C_{19}H_{39}COOH$), myristic acid ($C_{13}H_{27}COOH$), lauric acid ($C_{11}H_{23}COOH$), capric acid ($C_9H_{19}COOH$), caproic acid ($C_5H_{11}COOH$), oleic acid ($C_{17}H_{33}COOH$), caprylic acid ($C_7H_{15}COOH$), erucic acid ($C_{21}H_{41}COOH$), butyric acid (C_3H_7COOH), ethyl myristate ($C_{13}H_{27}COOC_2H_5$), ethyl oleate ($C_{17}H_{33}COOC_2H_5$), ethyl palmitate ($C_{15}H_{31}COOC_2H_5$), ethyl linoleate ($C_{17}H_{31}COOC_2H_5$), ethyl laurate ($C_{11}H_{23}COOC_2H_5$), ethyl linolenate, ($C_{17}H_{29}COOC_2H_5$), ethyl stearate ($C_{17}H_{35}COOC_2H_5$), ethyl arachidate ($C_{19}H_{39}COOC_2H_5$), ethyl caprilate ($C_7H_{15}COOC_2H_5$), ethyl caprate ($C_9H_{19}COOC_2H_5$), ethyl caproate ($C_5H_{11}COOC_2H_5$), ethyl butyrate ($C_3H_7COOC_2H_5$), triacetin ($C_9H_{14}O_6$), alpha tocopherol ($C_{29}H_{50}O_2$), beta tocopherol ($C_{28}H_{48}O_2$), delta tocopherol ($C_{27}H_{46}O_2$), gamma tocopherol ($C_{28}H_{48}O_2$), benzyl alcohol (C_7H_8O), benzyl benzoate

($C_{14}H_{12}O_2$), methylphenol (C_7H_8O), di-n-butyl sebacate ($C_{18}H_{34}O_4$), diethylphthalate ($C_{12}H_{14}O_4$), glyceryl monooleate ($C_{21}H_{40}O_4$), lecithin, medium chain triglycerides, mineral oil, petrolatum, and liquid paraffines.

23. Mixture according to one of the claims 1 to 22, characterized in that it is divided into a powder component and a liquid component, whereby

A) said powder component comprises the powder component of said two-component bone cement and a polysaccharide in powder form; and

B) said liquid component comprises the liquid component of said two-component bone cement and an aqueous solution of said X-ray contrast agent.

24. Mixture according to one of the claims 1 to 23, characterized in that the third component is a freshly mixed calcium phosphate cement paste.

25. Mixture according to one of the claims 1 to 24, characterized in that the size of all powder particles of the mixture are smaller than 300 micrometers, preferably smaller than 250 micrometers.

26. Mixture according to one of the claims 1 to 25, characterized in that the size of at least 80 % of all powder particles is in the range of 50 to 300 micrometers, preferably in the range of 80 to 250 micrometers.

27. Mixture according to one of the claims 1 to 26, characterized in that it hardens within 7 to 10 minutes, preferably within 8 to 9 minutes after mixing of its components.

28. Mixture according to one of the claims 1 to 27, characterized in that the hardened mixture has a Young's modulus of elasticity in the range of 10 to 2800 MPa, preferably in the range of 100 to 700 MPa.

29. Mixture according to one of the claims 1 to 28, characterized in that it further comprises an osteoinductive substance, preferably in its third component.

30. Mixture according to claim 29, characterized in that said osteoinductive substance is chosen from the following group of substances:

a) bone morphogenetic proteins, preferably BMP2, BMP4 or BMP7;
b) TGFb-3 (transforming growth factor) or IGF-1 (insulin-like growth factor);
c) plateled-derived growth factor (PDGF);
d) parathyroid hormone (PHT) and parathyroid hormone-related protein (PTHrP);
e) sexual hormones, in particular estrogen; and
f) prostaglandin.

31. Mixture according to one of the claims 1 to 30, characterized in that it further comprises an antiresorptive substance, preferably in its third component.

32. Mixture according to claim 31, characterized in that the antiresorptive substance is a bisphosphonate.

33. Mixture according to one of the claims 1 to 32, characterized in that it further comprises an anabolic substance, a parathyroid hormone (PTH) or an estrogene.

34. Mixture according to one of the claims 1 to 28, characterized in that it further comprises a hydrogen pump inhibitor, preferably basilomycin A1.

35. Use of an injectable bone cement mixture with the property to become porous after hardening in situ, for treating osteoporosis.

36. Use of an injectable bone cement mixture with the property to become porous after hardening in situ, for filling bone defects.

37. Use of an injectable bone cement mixture with the property to become porous after hardening in situ, as a carrier for an agent for the treatment of osteoporosis.

38. Method for preparing an injectable mixture for substituting bone tissue in situ according to one of the claims 1 to 34 comprising the following steps:

A) the two components of the bone cement are mixed first; and subsequently
B) the obtained mixture is dispersed in the third component.

39. Method for preparing an injectable mixture for substituting bone tissue in situ according to one of the claims 1 to 34 comprising the following steps:

A) the two components of the bone cement are mixed first; and subsequently

B) the third component is dispersed in the mixed two-component bone cement.

40. Method for preparing an injectable mixture for substituting bone tissue in situ according to one of the claims 1 to 34 comprising the following steps:

A) Mixing separately a two-component powder/liquid bone cement;

B) Mixing separately a two-component calcium phosphate cement;

C) Adding the separately mixed and still pasty two-component calcium phosphate cement to said separately mixed and still pasty two-component bone cement.

41. Method according to one of the claims 38 to 40, characterized in that said third component is dispersed into the two-component bone cement in such a way that the mean diameter of droplets of the third component dispersed in the two-component bone cement is less than 1 mm, preferably less than 0.5 mm.

AMENDED CLAIMS

[Received by the International Bureau on 04 August 2003 (04.08.03): original claims 35-37 replaced by amended claims 35-37 (1 pages)]

30. Mixture according to claim 29, characterized in that said osteoinductive substance is chosen from the following group of substances:

a) bone morphogenetic proteins, preferably BMP2, BMP4 or BMP7;
b) TGFb-3 (transforming growth factor) or IGF-1 (insulin-like growth factor);
c) plateled-derived growth factor (PDGF);
d) parathyroid hormone (PHT) and parathyroid hormone-related protein (PTHrP);
e) sexual hormones, in particular estrogen; and
f) prostaglandin.

31. Mixture according to one of the claims 1 to 30, characterized in that it further comprises an antiresorptive substance, preferably in its third component.

32. Mixture according to claim 31, characterized in that the antiresorptive substance is a bisphosphonate.

33. Mixture according to one of the claims 1 to 32, characterized in that it further comprises an anabolic substance, a parathyroid hormone (PTH) or an estrogene.

34. Mixture according to one of the claims 1 to 28, characterized in that it further comprises a hydrogen pump inhibitor, preferably basilomycin A1.

35. Use of an injectable mixture according to one of the claims 1 to 34 for treating osteoporosis.

36. Use of an injectable mixture according to one of the claims 1 to 34 for filling bone defects.

37. Use of an injectable mixture according to one of the claims 1 to 34 as a carrier for an agent for the treatment of osteoporosis.

38. Method for preparing an injectable mixture for substituting bone tissue in situ according to one of the claims 1 to 34 comprising the following steps:

A) the two components of the bone cement are mixed first; and subsequently
B) the obtained mixture is dispersed in the third component.

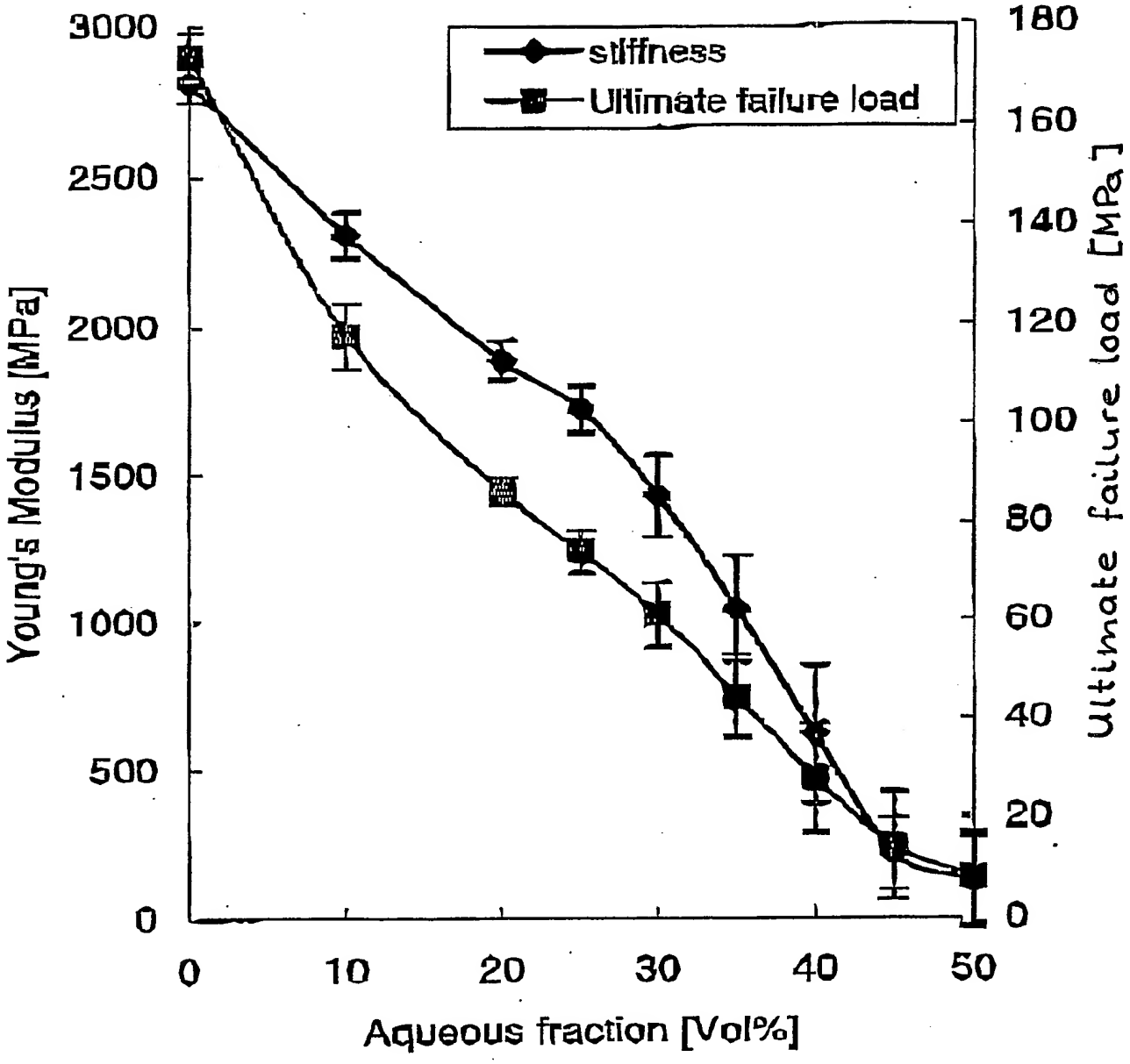
stiffness
Ultimate failure load
Young's Modulus [MPa]
Ultimate failure load [MPa]
Aqueous fraction [Vol%]
3000
2500
2000
1500
1000
500
0
180
160
140
120
100
80
60
40
20
0
0
10
20
30
40
50

Fig. 1

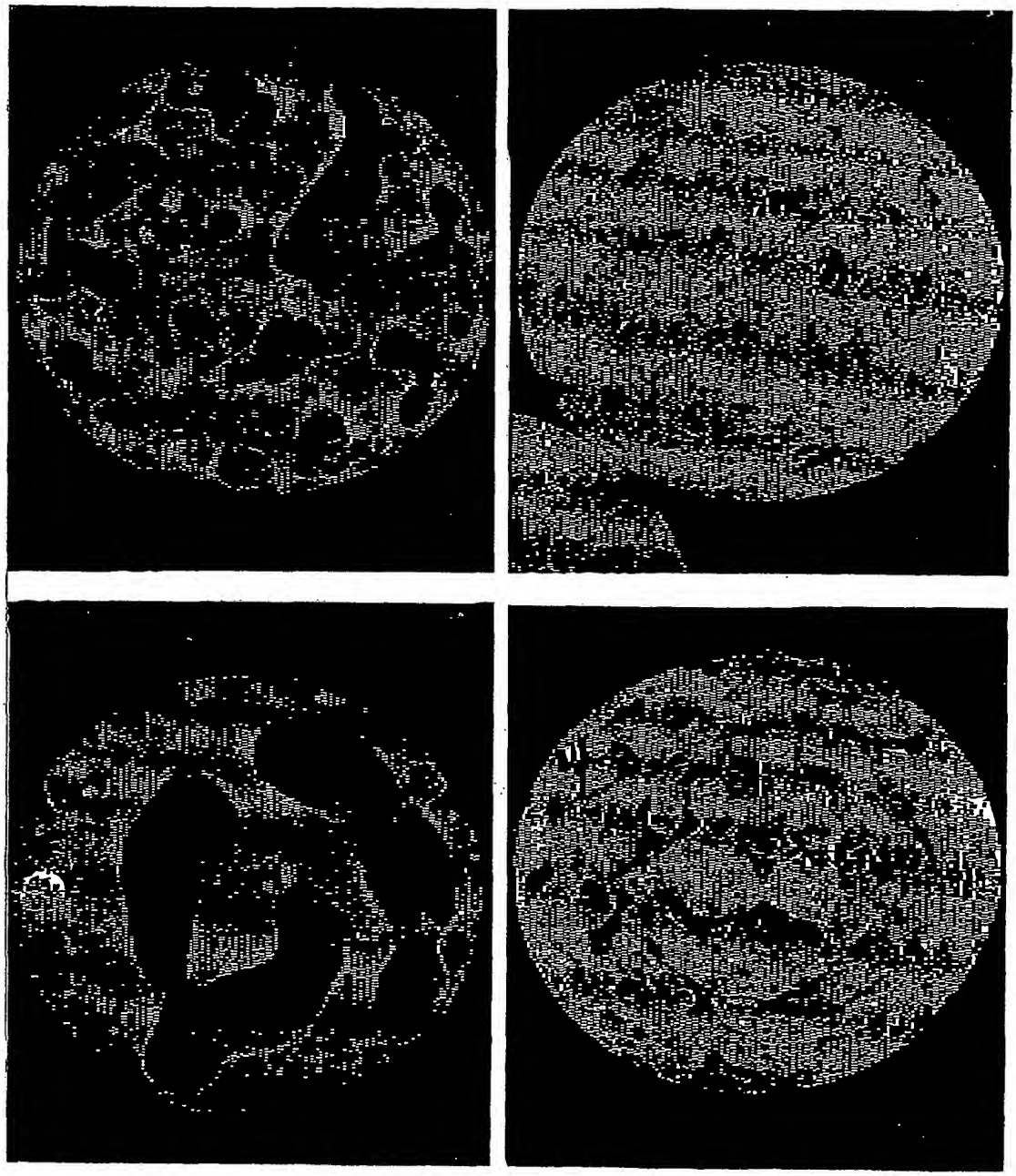

Fig. 2

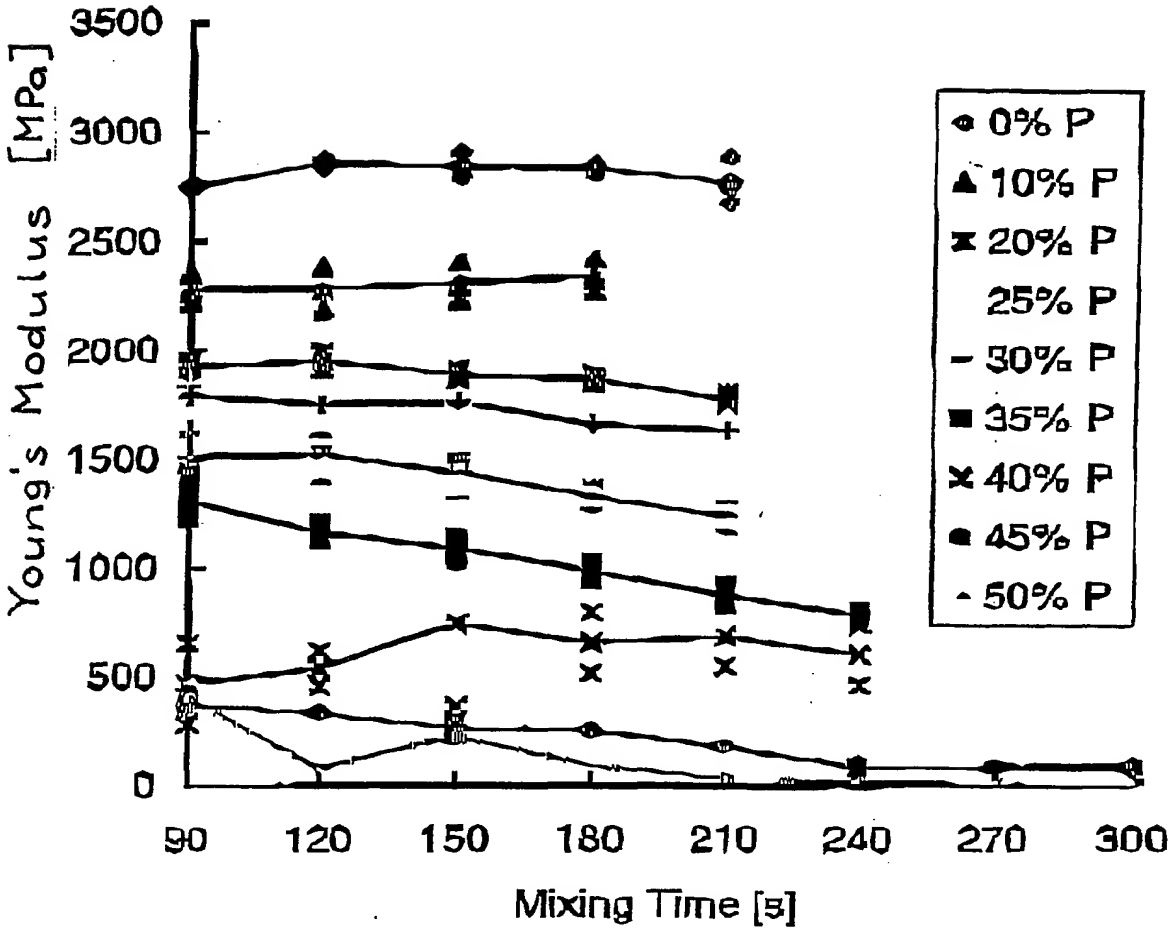
Young's Modulus [MPa]
3500
3000
2500
2000
1500
1000
500
0
90
120
150
180
210
240
270
300
Mixing Time [s]
0% P
10% P
20% P
25% P
30% P
35% P
40% P
45% P
50% P

Fig. 3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CH 03/00105

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L24/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 093 576 A (DEWIJN JOOST ROBERT) 6 June 1978 (1978-06-06) cited in the application abstract column 2, line 56 -column 3, line 8	1-34, 38-41
Y	BRUENS MARCO L ET AL: "Porous polymethylmethacrylate as bone substitute in the craniofacial area." THE JOURNAL OF CRANIOFACIAL SURGERY. UNITED STATES JAN 2003, vol. 14, no. 1, January 2003 (2003-01), pages 63-68, XP009008805 ISSN: 1049-2275 abstract "materials and methods"	1-34, 38-41

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 April 2003	24 07 2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Pilling, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CH 03/00105

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 62570 A (LIDGREN LARS AAKE ALVAR ;BONE SUPPORT AB (SE)) 9 December 1999 (1999-12-09) abstract page 2, line 7 - line 22 page 4, line 11 - line 16 page 4, line 22 - line 30 ---	1-34, 38-41
Y	DEB S ET AL: "Radiopacity in bone cements using an organo-bismuth compound" BIOMATERIALS, ELSEVIER SCIENCE PUBLISHERS BV., BARKING, GB, vol. 23, no. 16, August 2002 (2002-08), pages 3387-3393, XP004359626 ISSN: 0142-9612 abstract -----	1-34, 38-41

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CH 03/00105

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-34, 38-41

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CH 03/00105

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-34,38-41

   injectable mixture for substituting bone tissue comprising (i) a self hardening powder/liquid bone cement (ii) a liquid that is non-miscible with the cement paste and can be washed out of the cement paste after hardening leaving a porous bone substituting material and (iii) an organic X-ray contrast agent; methods for the preparation thereof

2. Claims: 35-37

   use of an injectable bone cement that can become porous after hardening for treating osteoporosis and/or filling bone defects

On the basis of the present description (see the final paragraph on present page 1 to page 2) it appears that the injectable mixture claimed in INVENTION SUBJECT 1 aims to overcome problems associated with washing out of inorganic X-ray contrast agents from prior art porous bone cements (such as those described in US-A-4093576). Thus, the problem to be solved in respect of INVENTION SUBJECT 1 is "how to provide X-ray contrasting and porous bone cement compositions that avoid problems of washing out of X-ray contrast agent(s)". The Applicant has solved this problem by providing an injectable mixture comprising (i) a self hardening powder/liquid bone cement (ii) a liquid that is non-miscible with the cement paste and can be washed out of the cement paste after hardening leaving a porous bone substituting material and (iii) an ORGANIC X-ray contrast agent.

Since the uses of INVENTION SUBJECT 2 do not essentially involve ANY contrast agent, it is considered that the objective technical problem to be solved in this case must be different to that mentioned above. Thus, there can be no single general inventive concept within the meaning of Rule 13.1 PCT to link the subject matter of INVENTION SUBJECTS 1 and 2. Moreover, since bone cements with the property to become porous after hardening in situ are clearly known (see, for example US-4093576 cited by the Applicant), there can be no special technical feature(s) linking the subject matter of Claim 1 with any of Claims 35 to 37 (Rule 13.2 PCT).

Moreover, the Applicant is warned that the ISA is aware of many disclosures involving bone cements comprising porosifiers in general. Hence, the Applicant should consider carefully the advisability of filing further processing fees in respect of INVENTION SUBJECT 2.

A search of INVENTION SUBJECT 2 would have involved significant additional searching efforts.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CH 03/00105

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4093576 A	06-06-1978	CH 611150 A	31-05-1979
		AT 338429 B	25-08-1977
		AT 307075 A	15-12-1976
		DE 2518153 A	28-10-1976
		GB 1533283 A	22-11-1978
		JP 1442309 C	08-06-1988
		JP 51124095 A	29-10-1976
		JP 62051629 B	30-10-1987
		NL 7600778 A,B,	20-10-1976
WO 9962570 A	09-12-1999	SE 511087 C	02-08-1999
		AU 4664299 A	20-12-1999
		EP 1079867 A	07-03-2001
		SE 9801901 A	02-08-1999